

REMARKS

Entry of this Amendment is proper under 37 C.F.R. §§ 1.111 and 1.114 given the request for continued examination under 37 C.F.R. § 1.114 submitted herewith. Applicants request reconsideration in view of the above amendments, following remarks, and attached Declaration under 37 C.F.R. § 1.132.

1. Interview

The Office is respectfully requested to contact the undersigned representative for an interview further discussion in view of the presently submitted amendments, remarks and Declaration prior to preparing its response.

2. Status of the Claims

Claims 1 and 3-6 stand pending and rejected.

3. Priority

Applicants note that the Office has asserted that the effective filing date of the claims is no earlier than the filing date of PCT/JP2005/05786, *i.e.*, March 26, 2005, because no English language translation was provided for the Japanese priority application, JP 2004-107512, which was filed March 31, 2004.

Applicants attach hereto a verified English translation of JP 2004-107512. By perfecting priority with this translation, Applicants claim benefit of the filing date of March 31, 2004. *See* M.P.E.P. § 706.02(b).

3. Rejection of the Claims Under 35 U.S.C. § 103(a)

3.1. Rejection of claims 1, 3-4, 6-9, and 11

The Office maintains the rejection of claims 1, 3-4, and 6 over the following three references:

- 1) **Certik M. *et al.*, *Desaturase-Defective Fungal Mutants: Useful Tools for the Regulation and Overproduction of Polyunsaturated Fatty Acids*, 16 TRENDS**

BIOTECHNOL. 500 (1998) [hereinafter "Certik"];

- 2) **Ueda R.**, *RNAi: A New Technology in the Post-Genomic Sequencing Era*, 15 J. NEUROGENETICS 193 (2001) [hereinafter "Ueda"]; and
- 3) **Mackenzie D.A. et al.**, *Isolation and Use of a Homologous Histone H4 Promoter and a Ribosomal DNA region in a Transformation Vector for the Oil-producing Fungus Mortierella alpina*, 66 APPL. ENVIRON. MICROBIOL. 4655 (2000) [hereinafter "Mackenzie"].

Certik relied upon for allegedly teaching that desaturase-defective *Mortierella alpina* mutants are useful to produce polyunsaturated fatty acids (PUFAs). Page 3, Office Action mailed April 7, 2009. Ueda allegedly teaches RNAi as a means of selectively inhibiting expression of genes that are conserved across plants, animals, and fungi. *Id.*, pages 3-4. Mackenzie allegedly teaches delivering genetic material to achieve stable expression in *Mortierella*. *Id.*, page 4.

The Office alleges that a skilled artisan, in view of Certik, Ueda, and Mackenzie, would have been motivated to employ RNAi to inhibit the activity of *M. alpina* desaturases. *Id.* Additionally, the Office asserts that one would have had a reasonable expectation of success in view of (1) Ueda's teaching that RNA interference has been known to function in fungi, and (2) Mackenzie's teaching that vectors and techniques are available for establishing stable expression of heterologous genes in *M. alpina*. *Id.*

In Amendment / Response filed March 16, 2009, Applicants argue that none of the references teaches a co-suppression method as recited. The Office discounts the arguments, alleging that (1) the RNAi method and the co-suppression method are recited as alternatives; and (2) the RNAi method is a species of the genus of phenomena recognized as co-suppression. Page 8, Office Action mailed April 7, 2009.

Applicants further argue that there was no reasonable expectation of success in combining the cited references to suppress a specific gene in *Mortierella* through either an RNAi method or a co-suppression method, because there has been no report as to the effectiveness of the RNAi method in lipid producing *Mortierella* at the priority date of the present application. The Office asserts that this argument was unpersuasive and unsupported, alleging that a

reasonable expectation of success required for *prima facie* obviousness differs from the certainty of success. The Office further alleges that the existence of conserved RNAi pathway across phylogenetic kingdoms, as taught by Ueda, would have provided a reasonable expectation that (1) the fungal species *M. alpina* would have a functional RNAi pathway, and (2) one could carry out RNAi in this species. Pages 9-10, Office Action mailed April 7, 2009.

Applicants had also argued in March 16, 2009 Amendment / Response that the recited methods are capable of fine-tuning the level of suppression, which amounts to unexpected results. The Office discounts the argument, referring to Ueda's teaching that the RNAi method is known to result in incomplete inhibition. *Id.*, pages 10-11.

Applicants traverse the rejection as it applies to claims 1, 3-4, and 6. Claims 7-9 and 11 stand cancelled thereby mooted the rejection as to those claims.

A finding of obviousness under 35 U.S.C. § 103 requires a determination of the scope and content of the prior art, the differences between the invention and the prior art, the level or ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966); *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 82 U.S.P.Q.2d 1385 (2007). When determining whether a claim is obvious, the Office must make "a searching comparison of the claimed invention—including all its limitations—with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572, 37 U.S.P.Q.2d 1127, 1133 (Fed. Cir. 1995). Further, "obviousness requires a suggestion of *all* limitations in a claim." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342, 68 U.S.P.Q.2d 1940, 1947 (Fed. Cir. 2003) (emphasis added). Once the scope and content of the prior art are determined, the relevant inquiry is whether the prior art suggests the invention, and whether one of ordinary skill in the art would have had a reasonable expectation that the claimed invention would be successful. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); *Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57,528. This includes assessing the references for what they teach as a whole and not particulate dissection of

a reference for piecemeal hindsight determinations of obviousness through the benefit of Applicants' own specification as guidance.

Contrary to the Office's position, the information at the time of filing would not have provided the skilled artisan with a reasonable expectation of success that the claimed breeding method would have worked.

(1) It was not possible at the time to predict at what level the precursors would accumulate. Declaration, ¶ 16. Accordingly, it would not have been possible to predict the fatty acid accumulation given co-suppression of the gene.

(2) In the case of the $\Delta 6$ fatty acid desaturase (¶¶23-25 Declaration), there are two genes in *Mortierella*. It was unpredictable at the time whether both genes could be co-suppressed using a construct based on the sequence of only one of the two genes. Declaration, ¶26.

(3) For the genes encoding desaturases, it would not have been reasonably been expected that suppression of a lipid metabolism gene in *Mortierella* would have worked by using an RNAi method or by using a co-suppression method. See Declaration, $\Delta 5$ fatty acid desaturase (¶¶14-16 Declaration), $\Delta 12$ fatty acid desaturase (¶¶17-19, Declaration), GLELO (¶¶20-22 Declaration), and $\Delta 6$ desaturase (¶¶ 23-26).

(4) The amount of linolenic acid produced by the $\Delta 6$ fatty acid desaturase was statistically significant and unexpected. Declaration ¶ 26.

Applicants provide the following evidence showing *even if* RNAi pathways exist in fungi generally, it does not provide a reasonable expectation that:

- 1) the RNAi pathway exists in a particular fungal species, and
- 2) a skilled artisan could carry out RNAi-mediated suppression in a particular fungal species
- 3) with any expectation of success given that it may not even be present.

In support of this argument, Applicants directed the Office to the post-filing non-patent references of (1) **Proudfoot** N. and Gullerova M., *Gene Silencing CUTs Both Ways*, 131 CELL 649 (2007) (Annex I) [hereinafter "Proudfoot"]; and (2) **Nakayashiki** H. and Nguyen Q.B.,

RNA Interference: Roles in Fungal Biology, 11 CURR. OPIN. MICROBIOL. 494 (2008) (Annex II)
[hereinafter "Nakayashiki"]. Proudfoot states:

In the fission yeast *Saccharomyces pombe*, gene silencing has been shown unexpectedly to involve the RNA interference (RNAi) pathway and in particular the RNase III enzyme Dicer... However, the budding yeast *S. cerevisiae* seems bereft of RNAi-mediated gene regulation, as it lacks Dicer,
ΔPage 649, bottom parts of col. 1 and col. 3, Proudfoot.

Similarly, Nakayashiki states:

In some fungal species, such as *S. cerevisiae* and *Ustilago maydis*, the entire RNA silencing machinery appears to be lost, indicating that RNA silencing pathways may be dispensable for fundamental metabolism and development in fungi. Interestingly, in *Ustilago hordei*, a close relative to *U. maydis*, RNA silencing has been demonstrated. Therefore, **the loss of the RNA silencing machinery seems to sporadically occur in the fungi kingdom**, as previously shown in the protest *Trypanosomes*. In support of this, *A. nidulans* appears to be 'losing' one of the two copies of dicer and argonaute genes while, intriguingly, its close relatives *Aspergillus oryzae* and *Aspergillus flavus* have likely gained extra copy of dicer and argonaute genes, possibly by gene duplication. (Emphasis added).

Page 498, bottom portion of the left col. and upper portion of the right col. Proudfoot and Nakayashiki combined teach that RNAi machinery cannot be expected in every fungal species, because it may be "sporadically" lost in certain fungal species, such as *Saccharomyces cerevisiae* and *Ustilago maydis*. This loss can occur even while the machinery remains intact even among closely related species, such as *S. pombe* and *U. maydis*, respectively.

Applicants submit herewith the Declaration of Masako Fukushi-Mizutani under 37 C.F.R. § 1.132. Applicants note that an expert's evaluation concerning unexpected results is entitled to more weight than that of a layman, and it is improper for the Patent Office to substitute its judgment for that of an established expert in the art. *In re Zeidler*, 215 U.S.P.Q. 490, 494 (C.C.P.A. 1982). Additionally "one way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 34 U.S.P.Q.2d 1684, 1687 (Fed. Cir. 1995). The Declaration describes that it was unexpected that the RNAi co-suppression

worked for all of the genes encoding desaturases. Additionally, with at least the $\Delta 6$ fatty acid desaturase, there was an additional unexpected results, wherein the production of direct or indirect products produced by the suppression of the $\Delta 6$ fatty acid desaturase was reduced by more than 50% as compared to controls, and the amount of substrate (18:2(n-6)) was increased at least 2-fold. Declaration, ¶ 26.

Accordingly, a skilled artisan could not have had a reasonable expectation that the RNAi machinery existed in a particular fungal species, *i.e.*, *Mortierella*. Declaration, ¶11. While Proudfoot and Nakayashiki were published after the filing, their teachings should not be discounted. The articles further evince that even after the filing date, a reasonable expectation of success was not supported scientifically. Declaration, ¶12. The cited references relied upon by the Office do not provide a reasonable expectation of success that this putative combination could have successfully worked, *i.e.*, achieving suppression of a lipid metabolism gene in *Mortierella* through either an RNAi method or a co-suppression method. Declaration, ¶ 9.

For the reasons discussed above, claims 1, 3-6 are nonobvious over the art as there simply was no expectation of success that the claimed combination in the methods would have worked. Additionally, Applicants have provided evidence of unexpected results. The amended claims are thus non-obvious over cited references. *See Vaeck*, 947 F.2d at 493, 20 U.S.P.Q.2d at 1442. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

3.2. Rejection of claims 1 and 3-8

The Office maintains the rejection of claims 1 and 3-8 over **Takeno S. *et al.***, *Establishment of an Overall Transformation System for an Oil-Producing Filamentous Fungus, Mortierella alpina* 1S-4, 65 APPL. MICROBIOL. BIOTECHNOL. 419 (2004) [hereinafter “**Takeno**”] as applied to claim 1 and further in view of Ueda and Mackenzie.

Applicants traverse. The legal basis for determining obviousness is discussed in Section 3.1. *supra*. Applicants note that the rejection stands only for claims 1 and 3-6 as claims 7-8 stand canceled.

Each claim recites a method of breeding lipid producing *Mortierella* by suppressing

expression of a lipid metabolism gene with an RNAi method or a co-suppression method. With the submission herewith of a verified English translation of JP 2004-107512, Applicants have perfected priority to the instant Japanese application and the filing date of March 31, 2004. As the perfected filing date antedates the on-line publication date of Takeno, May 12, 2004, Takeno is no longer available as a prior art reference.

Ueda and Mackenzie, alone or combined, fail to teach suppressing expression of a lipid metabolism gene in *Mortierella*, for at least the reasons set forth in Section 3.1, *supra*. The Office fails to adduce a *prima facie* case of obviousness, because the alleged prior art references fail to teach or suggest *all* claim elements. *CFMT, Inc.*, 349 F.3d at 1342, 68 U.S.P.Q.2d at 1947. Additionally, the rejection of claims 7-8 is mooted by their cancellation.

Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of claims.

3.3. Rejection of Claim 5

The Office maintains the rejection of claim 5 over Certik and Mackenzie as applied to claims 1, 3, 4, 6-9, and 11, and further in view of **White** T.C. *et al.*, U.S. Patent No. 6,939,704 [hereinafter “White”]. White allegedly teaches that filamentous fungi could be transfected by calcium chloride treatment, electroporation, or particle bombardment. Page 7, Office Action. The Office admits that the combination of Certik, Ueda, and Mackenzie fails to teach gene delivery by electroporation or particle bombardment. *Id.*, at page 6. Their teachings are summarized *supra*. The Office apparently applies White to cure the admitted defect.

Applicants traverse to the extent that the rejection is maintained as to amended claim 5. The legal basis for obviousness is discussed in Section 3.1, *supra*.

White purportedly teaches methods of transfection for filamentous fungi. However, White fails to teach suppressing the expression of a lipid metabolism gene in *Mortierella* through an RNAi method or a co-suppression method, which is presently recited in each claim. As discussed in Section 3.1, *supra*. Certik, Ueda, and Mackenzie, when read either alone or combined, fail to provide a reasonable expectation of success to suppress the expression of a lipid metabolism gene in *Mortierella* through an RNAi method or a co-suppression method as

argued *supra*. The addition of White fails to cure these defects inherent to Certik, Ueda, and Mackenzie. Thus, the combination of the four references fails to adduce a *prima facie* case of obviousness.

Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

In view of the above, the Office is respectfully request to withdraw all obviousness rejections and allow claims 1 and 3-6.

CONCLUSION

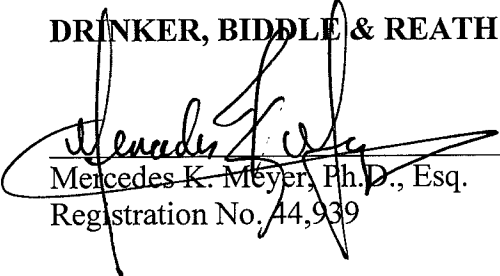
Should the Examiner have any questions or comments regarding Applicants' amendments or response, please contact Applicants' undersigned representative at (202) 842-8821. Furthermore, please direct all correspondence to the below-listed address.

In the event that the Office believes that there are fees outstanding in the above-referenced matter and for purposes of maintaining pendency of the application, including Notice of Appeal should one be necessary, the Office is authorized to charge the outstanding fees to Deposit Account No. 50-0573. The Office is likewise authorized to credit any overpayment to the same Deposit Account Number.

Respectfully submitted,

DRINKER, BIDDLE & REATH LLP

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